Accelerating the Pace of Chemical Risk Assessments Workshop
September 14 – 15, 2016
US Environmental Protection Agency
Washington, DC

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The NICNAS Inventory Multi-tiered Assessment and Prioritisation (IMAP) Program

Kerry Nugent, National Industrial Chemicals Notification and Assessment Scheme, Australia

The Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework was established by the Australian Government's National Industrial Chemicals Notification and Assessment Scheme (NICNAS) to accelerate the assessment of risks posed to human health and the environment by previously unassessed chemicals. The objectives of IMAP were the identification and rapid assessment of existing chemicals of concern, leading to enhancements in chemical safety information flow and chemicals management

IMAP comprises three tiers of assessment, with the assessment effort increasing with each tier. The initial two tiers combine assessment and prioritisation. Tier I utilises a matrix-based sorting step, which is focussed on identifying chemicals of sufficiently low regulatory concern as to not require further assessment or other use of resources. Tier II involves identification of relevant data, and preparation of a brief report to characterise the likely risks. The Tier II assessments also examine whether appropriate risk management measures already exist, and whether the available data are sufficient to justify relevant risk management measures. Tier III comprises assessment of any critical questions identified in the Tier II examination of the available data.

For the majority of chemicals, IMAP assessments were undertaken in the absence of any Australian use or volume data, which limited the extent to which quantitative assessment could be carried out. In addition, only approximately 10% of Tier II assessments had data for all standard toxicological endpoints considered.

This presentation will focus on the human health aspects of IMAP, which also includes environmental assessment. The IMAP matrix used for human health at Tier I was developed to account for the lack of quantitative data, together with the need to consider a wide range of hazards. Unlike the Risk21 matrix, which uses effect levels and doses as its axes, the IMAP matrix used surrogates for these quantities, described as hazard bands and exposure bands.

At Tier II, the absence of access to detailed exposure information prevented the use of margin of safety approaches. However, risk management recommendations were able to be made based on qualitative risk assessment approaches for a significant number of chemicals.

The challenges of the use of non-standard data sources, including read-across, grouping and QSAR, in as part of the IMAP framework will be discussed. The extent to which non-quantitative risk assessment can be used to inform risk management will also be addressed in the presentation.

New Approach Methodologies to Support Canada's Chemicals Management Plan

Tara Barton-Maclaren, Health Canada, Canada

Under the Chemicals Management Plan (CMP), the Government of Canada is committed to addressing 4,300 existing substances by 2020. Moving forward into the third phase of the CMP (2016-2020) and beyond, a key challenge is assessing the potential for risk to human health of substances that have limited to no toxicological data. The *Canadian Environmental Protection Act 1999* (CEPA) requires the incorporation of weight-of-evidence and precaution and that risk assessment conclusions are protective of human health and the environment. In addition, the assessment methods must be able to accommodate substances and substance groupings with varying amounts and types of information, including emerging scientific knowledge and assessment approaches. As such, Health Canada has an

interest in establishing proof of concept for the application of new approach methodologies, including High Throughput Screening (HTS) data, into risk assessment activities under the CMP. Through active collaborations with the Environmental Health Science and Research Bureau at Health Canada, as well as with international partners (e.g. US EPA, OECD), progress has been made on the interpretation of emerging data and NAMs for a range of uses in risk assessment from priority setting to informing decision-making.

Canada's presentation will provide an overview of the various analyses that have been conducted or are currently in progress that explore the use of NAMs in order to gain confidence for broader application in risk assessment activities under CEPA. A particular focus will be on an ongoing joint Health Canada-US EPA National Centre for Computational Toxicology (NCCT) case study developed to gain experience using a subset of 21 substituted phenols that will be addressed under phase 3 of Canada's CMP. A human health related concern with phenols is that they can have the potential to be estrogenic. Bisphenol A (BPA) is a typical example of a phenolic estrogen. The selected CMP phenolic compounds contain substituents at various positions relative to the hydroxyl group. The type of substituent and position relative to the hydroxyl group is anticipated to have an impact on the estrogenic potential and potency. This case study addresses several key elements including investigating systematic approaches for identifying valid source analogues and assessing their resulting read-across performance as well as exploring the utility of HTS data to substantiate chemical categories formed and reducing uncertainties associated with the traditional read-across for apical effects. (Q)SARs such as those derived under the Collaborative Estrogen Receptor Activity Prediction Project (CERAPP) are also integrated into the weight of evidence assessment. Where the required data was available for target CMP substituted phenols, the bioactivity exposure ratio (BER) was compared with traditional margin of exposure (MOE) techniques in order to further examine the utility of the HTS data to predict potential level of concern for human health effects for the purposes of prioritisation and risk assessment.

The case study is still ongoing but work completed to date shows that the approach is promising for developing a weight of evidence assessment for the estrogenicity activity for the target CMP substituted phenols.

Current Chemical Risk Assessment Practices in ECHA – Challenges and Opportunities

Mike Rasenberg, European Chemical Agency, European Union

TBD

Connecting Exposure, Toxicokinetics, and Toxicity: Towards Animal Free Risk Assessment in Food Safety?

Jean-Lou Dorne, European Food Safety Agency, European Union

Human risk assessment of chemicals in the food safety area involves the classic steps to bring hazard and exposure together for risk characterisation. Ideally, sound hazard identification and hazard characterisation requires a quantitative understanding of the mode of action i.e. toxicokinetics (TK) and toxicodynamic (TD) processes in humans for compounds entering the human body via the oral route. A key issue is to move away from empirical approaches using test species and move towards human relevant mechanistic approaches. This presentation explores some research and collaborative efforts at the European Food Safety Authority (EFSA) aiming to move towards mechanistic alternatives to animal testing in the food safety area through the developments of data-based and biologically-driven tools.

EFSA has published over 2000 risk assessments for over 4000 substances in the human health, animal health and the ecological areas since its creation in 2002. The development of "Openfoodtox": EFSA's

open source database (12/2016), structured using OECD harmonised templates, and the nature of the summary hazard data available for individual substances is briefly discussed.

Since pesticides are of high concern and data rich chemicals, they could be used for testing advantages and limitations of new tools. In this context, EFSA ongoing and planned activities are presented including 1. A database of validated endpoints for risk assessment covering human health and the environment. 2. Use of non-animal strategies for addressing metabolites in the new EFSA guidance to define pesticides residues (chemicals to be included in the assessment of consumer risks). 3. AOPs and identification of risks of human diseases not sufficiently covered by animal experimental studies. 4. Realistic environmental risk assessments addressing landscape and spatial variability.

Collaborative research activities to develop an open source TK platform are presented with a focus on the basic principles to develop tools and models for human risk assessment. These include data collection on human variability in absorption, distribution, metabolism, excretion processes and the use of human *in vitro* and *in silico* tools to support the application of quantitative *in vitro* to *in vivo* extrapolation in food safety.

Ultimately, supporting risk assessors and decision makers requires an understanding of their practical needs (i.e., problem formulation, knowledge available for a chemical, resources and time available). Some examples of generic scenarios (data poor, regulated compound, data rich compound) and options to map and weigh evidence for exposure, hazard (TK/TD) and risk characterisation in the food safety area are illustrated. International cooperation between scientific advisory bodies throughout the world concludes as the corner stone to 1. translate 21st century toxicological research into real life case studies, harmonised methodologies, and tools and 2. train the current and next generation of risk assessors.

Computational Risk Assessment for Mixtures of Chemicals: The Case of Aromatase Inhibitors

Phillippe Hubert, INERIS, France

Within the framework of EUROMIX project, the size of potential effects of random mixtures of aromatase inhibitors on the dynamics of women's menstrual cycle has been quantified through mathematical modeling and simulations. Combining computational toxicology with ExpoCast exposure data and ToxCast assay data gives access to predictions of human health risks stemming from realistic exposures to chemical mixtures. Random exposures were simulated to millions of potential mixtures of up to 256 aromatase inhibitors. A pharmacokinetic model of intake and disposition of the chemicals predicted their internal concentration as a function of time (up to two years). A ToxCast aromatase assay provided concentration-inhibition relationships for each chemical. The resulting total aromatase inhibition was input to a mathematical model of the hormonal hypothalamus-pituitary-ovarian control of ovulation in women. Above 10% inhibition of estradiol synthesis by aromatase inhibitors, noticeable (eventually reversible) effects on ovulation were predicted. Exposures to individual chemicals never led to such effects. Typically, more than 10% of the combined exposures simulated had mild to catastrophic impacts on ovulation. The size of the effects predicted is consistent with an increased risk of infertility in women from daily life exposures to our chemical environment.

The results demonstrate the possibility to predict large scale mixture effects for endocrine disrupters with a predictive toxicology approach. It is suitable for high throughput ranking and risk assessment, and it illustrates benefits and limitations of an approach for using data bases and PK modeling.

Current Chemical Management and Prioritization in Japan

Jun Kanno, Ministry of Health, Welfare and Labour, Japan and Taisen Iguchi, Ministry of the Environment, Japan

TBD

Integrated Risk Assessment Methodology for Endocrine Disrupting Chemicals (IRAMe)

Kiyoung Lee, Seoul National University, Republic of Korea

Endocrine disrupting chemicals (EDCs) are emerging chemicals with possible adverse health effects from exposure to chemicals that can interfere with the endocrine system. The EDCs can be exposed through various exposure media and consumer products. With introduction of more chemicals with potential endocrine disrupting function, management of those chemicals is needed.

In this research for EDCs regulation in Korea, we will introduce several specific steps that can be useful for accelerating risk assessment.

1.) Prioritization of EDCs
With non-specific definition of EDCs, many organizations have their own list of EDCs. We developed prioritization method to identify priority EDCs using existing databases. The prioritization methods included human exposure, toxicity, and social concern. In addition to identification of priority EDCs from existing database, we are conducting biomonitoring to identify emerging EDCs. Based on prioritization and biomonitoring, we are constructing priority and emerging EDCs list.

2.) Toxicological application
Next step is to develop toxicological information of the EDCs. Although a few EDCs have toxicological information, majority of them do not have toxicity information especially endocrine related effects. We are applying two approaches. 1) bioinformatics analysis of pre-existing data generated from toxicogenomic studies, 2) *in vitro* toxicity comparison experiment.

Toxicogenomics are used to screen potential endocrine disrupting effects using existing database. For phthalate, NCBI GEO database was utilized. *In vitro* toxicity comparison is developed to determine relative potency factor based on well-known EDC.

3.) Integrated risk assessment for EDC chemical class
We performed the integrated risk assessment, at first, for phthalates and bisphenols, and will extend EDCs of target through biomonitoring in urines of susceptible population and chemical analysis of their surrounding environmental samples including indoor dust and air. We develop tentative reference dose (tRfD) which is the relative factor against DEHP, for emerging and alternative EDCs because their reference toxicity values are not developed yet, by conducing the comparative *in vitro* test using 3 different cell lines of H295R, MVRN, and GH3 (tier 1) and *in vivo* embryonic zebrafish assay (tier 2). Consequently, we can find the major source point for management strategy of not only conventional but emerging alternative EDCs.

Current Chemical Management and Prioritization in Taiwan

Steve (Yichen) Lin, Safety and Health Technology Center, Taiwan

The Occupational Safety and Health Act (OSHA) governed by the Ministry of Labor (MOL) and the Toxic Chemical Substances Control Act (TCSCA) governed by the Environmental Protection Administration (EPA), and several other regulations have been amended or developed to foster the safer use of chemicals to protect human health and environment. In 2009, Taiwan's MOL has incorporated relevant information nominated by industries and stakeholders to establish the very first national inventory,

Toxic Chemical Substance Inventory (TCSI), which was sequentially announced in December 2014. The second edition of TCSI also has been officially released in August 2015. The TCSI lists over 100,000 chemical substances, including the existing chemical nomination held by the MOL before 2014 and another 7,500 substances received and reviewed by the EPA while implementing the latest existing chemical nomination in 2015. This TCSI has become the cornerstone for further chemical management modernization in Taiwan. Moreover, it distinguished the existing chemical substances from new chemical substances within the registration scheme under both TCSCA and OSHA to obtain chemical safety information similar to EU REACH dossier. The strategies for MOL are to manage chemicals operated in workplace with unreasonable risk will be assigned as Control Chemicals in workplace. MOL are performing the screening step for chemicals' data collected from Priority Management Chemicals reporting process, and further tier 1 and tier 2 assessment will proceed to determine the different designated chemicals as required for chemical exposure for labors. Taiwan EPA has started the tier 0 screening, and decided which chemical substances with adequate GHS classification will be assigned to high, moderate, and low risk categories. If chemical substances with insufficient GHS classification, then the industry challenge program will be performed to evaluate chemicals hazard identification. Due to data gaps and more detail information are required for hazard identification for MOL or EPA, the new approach methods are evaluated to effectively fill in current lack data. Therefore, the all possible approach methods are potential to be considerate in further risk assessment in Taiwan chemical management programs.

Introduction to Agency for Science, Technology & Research (A*STAR)

Kenneth Lee, Agency for Science, Technology & Research, Singapore

The Agency for Science, Technology and Research (A*STAR) is Singapore's lead government agency for catalysing and supporting industry development. Pharmaceuticals, Biologics, Consumer Care, Food and Nutrition, and Specialty Chemicals are some of the industries that are well-established or have a growing presence in this city-state in the heart of South-East Asia, which has a market size of US$1.9 trillion. Multinationals like Procter & Gamble and Nestlé have major R&D centres in Singapore and are partners of A*STAR, which has 18 research institutes and 4,600 scientists spanning the life sciences, chemical sciences, engineering, and modelling and computational sciences.

Within a framework of responsible innovation, we are in the initial stages of building a programme to help advance safety science and health research with innovative, non-animal tools. The programme will draw on A*STAR's multidisciplinary capabilities to address the growing need for more reliable, robust, and predictive methods for safety and efficacy testing. We have recently embarked on a partnership with US EPA. Specifically, we are collaborating with US EPA's National Centre for Computational Toxicology (NCCT) on three topics around kidney, liver and developmental toxicity. We have also begun engaging proactively with regulatory agencies in Singapore and in the near future will broaden our outreach to other ASEAN countries. We welcome the opportunity to collaborate with other like-minded organisations.

Integrated Approaches to Testing and Assessment (IATA) Case Studies Project

Robert Diderich, Organisation for Economic Cooperation and Development (OECD), European Union

In an effort to gain experience in utilising Integrated Approaches to Testing and Assessment (IATA) in various regulatory contexts, the Hazard Assessment Programme at the OECD commenced an "IATA Case Studies Project" in 2015 with the objective to increase experience with the use of IATA by developing case studies, which constitute examples of predictions that are fit for regulatory use. The aim is to create common understanding of using novel methodologies and the generation of

considerations/guidance stemming from these case studies. It is envisioned that case studies within this project could be used as vehicles for further exploring the application and combination of AOPs, HTS, toxicogenomics and other *in vitro*/*in vivo* data. Information from this project will be made publicly available (http://www.oecd.org/env/ehs/risk-assessment/hazard-assessment.htm). Thus far countries and other stakeholders submitted and reviewed 4 case studies in 2015, and developed a considerations document of the learnings from the case studies. An additional 5 case studies are currently under review in 2016. Submission of case studies for 2017 is encouraged.

2015 Case Studies:

- *In Vitro* Mutagenicity of 3,3' Dimethoxybenzidine (DMOB) Based Direct Dyes [Canada and United States]
- Repeat Dose Toxicity of Substituted Diphenylamines (SDPA) [Canada]
- Hepatotoxicity of Allyl Ester Category [Japan]
- Bioaccumulation Potential of Biodegradation Products of 4,4'-Bis (chloromethyl)-1,1'-biphenyl [Japan]

2016 Case Studies:

- Repeated-Dose Toxicity of Phenolic Benzotriazoles [Japan]
- Pesticide Cumulative Risk Assessment & Assessment of Lifestage Susceptibility [United States]
- 90-Day Rat Oral Repeated-Dose Toxicity for Selected n-Alkanols: Read-Across [ICAPO]
- 90-Day Rat Oral Repeated-Dose Toxicity for Selected 2-Alkyl-1-alkanols: Read-Across [ICAPO]
- Chemical Safety Assessment Workflow Based on Exposure Considerations and Nonanimal Methods [JRC/BIAC]

The Frank R. Lautenberg Chemical Safety for the 21st Century Act

Jeff Morris, US Environmental Protection Agency, USA

On June 22, 2016, President Barack Obama signed into law the Frank R. Lautenberg Chemical Safety for the 21st Century Act, which amends the Toxic Substance Control Act (TSCA), the primary US chemicals management law. The amended TSCA includes such improvements as a mandatory requirement for US EPA to evaluate existing chemicals with clear and enforceable deadlines, and a new risk-based safety standard. It also includes important provisions for alternative testing and considering susceptible populations.

Case Example for Use of High Throughput and Computational Approaches in Decision Making for Endocrine Disruption Potential

Stan Barone[1], Kristan Markey[1], Carolina Pinto[2], Scott Lynn[1], Seema Schappelle[1], and Sharlene Matten[1]
[1]Office Science Coordination Policy, OCSPP, US EPA and [2]ORISE Fellow, USA

The Endocrine Disruptor Screening Program (EDSP) was established under authorities contained in the Food Quality Protection Act (FQPA) and the Safe Drinking Water Act (SDWA) amendments. As mandated by these statutes, the EDSP develops a screening program to determine whether certain substances may have endocrine activity in humans and wildlife. The US EPA has developed a two tiered approach for screening chemicals and pesticides. The Tier 1 battery is used to identify substances that have potential to interact with the estrogen, androgen or thyroid hormone pathways. The Tier 2 tests identify and establish dose response information for adverse effects for substances identified in the Tier 1 screening.

Additionally, EDSP is incorporating ToxCast high throughput screening data and computational models in the prioritization and screening of a chemical's potential to interact with the endocrine system in

humans and wildlife for a portion of the Tier 1 battery. This approach will allow nearly 20 times the current number of screenings to be performed while nearly eliminating animal testing, allowing the program to meet its goals with a relatively level budget. In coming years, OCSPP plans to expand this concept to screen for other endocrine and potentially non-endocrine endpoints. This technological breakthrough can massively expand OCSPP's ability to screen and assess chemical safety, including existing chemicals currently under evaluation, prior to seeking data from industry partners.

The EPA's EDSP is expanding the use of high-throughput assays and computational tools to prioritize and screen chemicals for potential endocrine bioactivity and exposure; in particular, the estrogen, androgen, or thyroid hormone pathways in humans and wildlife. The expanded use of these alternative testing methodologies increases the output of screening results and allows for greater coverage of the endocrine system. The vanguard efforts of the EDSP related to endocrine bioactivity will allow the OCSPP programs to apply these alternative testing methodologies to EDSP and non-EDSP-related evaluation of developmental neurotoxicity, immunotoxicity and other toxic effects.

These new approaches have been successfully used in a number of decision contexts. Most notably, the screening and prioritization of chemicals and pesticides through EDSP has resulted in the refinement of Tier 1 EDSP in vitro and in vivo tests and the availability of alternative testing procedures for the estrogen pathway. Other aspects of current implementation of alternative data have been leveraged in the development of AOP frameworks for prediction of adverse outcomes and use in weight of evidence analyses. However, key challenges remain in addressing acceptance of alternative data in different decision contexts. Some of these challenges relate to interpretation and extrapolation issues for alternative approaches including coverage of biological space, coverage of chemical space, false negatives associated with signal detection and metabolic potential, and in vitro to in vivo extrapolation.

The views expressed in this abstract do not necessarily reflect US EPA policy.

California's Approach to Evaluating and Incorporating New Methods in Prioritization and Risk Assessment

Gina M. Solomon, California Environmental Protection Agency, USA

California's data needs span a wide range of decision contexts, including: (1) Prioritization of chemicals for our Biomonitoring California program; (2) Quantitative risk assessment of pesticides, drinking water contaminants, waste sites, and toxic air contaminants under various statutes; and (3) Selection of chemical-product combinations for alternatives analysis under our Safer Consumer Products (SCP) Program. Recognizing the potential importance of new alternative methods (NAMs) for toxicity and exposure evaluation, the California Environmental Protection Agency (CalEPA) initiated in 2013 an intra-Agency effort to evaluate the utility of new alternative data in our programs.

Toxicologists and environmental scientists within CalEPA are working in teams to develop subject matter expertise in emerging methods, including ToxCast, Tox21, and various chemical use and exposure tools. We have published papers on some of our initial case studies, including on pesticides and phthalates, and a paper referring to its use in biomonitoring prioritization. Our Department of Pesticide Regulation is incorporating NAM data summaries into risk assessments to support weight-of-evidence determinations for pesticides, and the Office of Environmental Health Hazard Assessment is similarly using the data as part of mechanistic evaluations and in support of hazard trait and dose response assessment. SCP scientists are using emerging tools for chemical use and exposure potential to aid in selection of chemical-product combinations for evaluation.

NAMs have significant potential to aid in prioritization. For example, our Office of Environmental Health Hazard Assessment has created structural and functional groups of chemicals that have been

successfully prioritized for biomonitoring by our independent Scientific Guidance Panel. Examples of such groups include p,p'-bisphenols; non-halogenated aromatic phosphates; and synthetic polycyclic musks. NAM data have potential utility for supporting the identification and prioritization of chemical groups, and to support read-across evaluations for hazard trait identification and dose-response.

Greater detail about chemical functional uses, chemical roles throughout the supply chain, and exposure potential would be highly beneficial for prioritization, but such data are very limited. Exposure NAMs are generally not as developed as toxicity evaluation tools, but are nonetheless important to us as end-users.

In risk assessment, we have encountered some challenges with the new data, including failure of the alternative methods to identify key, established toxicity endpoints for some of our test-case pesticides, and limited ability to group phthalates according to common toxicity characteristics or provide relevant information on mode of action. These challenges suggest a need for caution prior to relying on alternative methods, especially when these methods are used to support a finding of absence of a hazard.

DAY 2 – THURSDAY, SEPTEMBER 15, 2016

Use of All Available Data in Accelerated Chemicals Assessment

John R. Bucher, National Toxicology Program, USA

Background: Advances in toxicology including alternative species, Tox 21, TSCA reform, and application of systematic review methods to environmental health information offer new opportunities to use diverse data in new ways for public health decisions. The National Toxicology Program (NTP) response to a brief contamination of the Charleston, West Virginia (WV) drinking water supply resulting from a chemical spill into source water provided a unique dataset to predict few health concerns.

Methods: Coal cleaning chemicals spilled into the Elk River were subjected to SAR analyses, and studied in bacterial mutagenicity, Tox21, *C. elegans*, zebrafish, and for teratology, genetic toxicity, and toxicogenomics in rats.

Approach: Results were modeled using benchmark dose analyses and compared to the drinking water advisory levels established by CDC at the time of the spill.

Results: SAR suggested concerns for development and irritancy. Results of Tox21, *C. elegans*, zebrafish, and genetic toxicity were largely negative. Toxicogenomics showed a lack of gene induction in pathways of toxicity concern in liver and kidney of rats. Teratology studies suggested only lower birth weights in rat pups.

Conclusions: Public health concerns were mainly for exposures to pregnant women in the Charleston area. The NTP data suggested few effects other than lower birth weights in rats. The state of WV subsequently studied birth weights in the Charleston area during the years before and following the spill. No effects were observed. Increasingly toxicology will need to balance potential human exposure levels with data from rapid studies establishing exposure levels that do not cause an effect, rather than the slow, exhaustive demonstration of levels that do cause apical outcomes. Systematic review methods, although not used in this case, can in the future help in focused problem formulation, comprehensive literature analysis and data integration across multiple evidence streams to use all available data.

Development of the RapidTox Decision Support Tool for 21st Century Chemical Risk Assessment

Russell Thomas, US Environmental Protection Agency, USA

The path for incorporating new approach methods and technologies into chemical risk assessment poses a diverse range of challenges including delivering the data in a useful way to risk assessors. The goal of the RapidTox project is to integrate a range of information related to chemical properties, fate and transport, hazard, mode-of-action, and exposure through an interactive on-line decision support tool in order to enable screening-level assessments to be performed for hundreds to thousands of chemicals. The data will be delivered as a tiered approach where traditional, high-quality data will be provided when available with lower tier data, including new approach methods, provided when higher tier data is not available. The RapidTox tool is being developed in close partnership with regulatory partners using a series of case studies. The first case study will use the tool to prioritize non-food use pesticidal inert ingredients for additional study. The second case study will quantitatively estimate screening level toxicity values with associated uncertainty for data poor chemicals at Superfund sites. The presentation will cover development of the RapidTox tool as an example of what chemical risk assessments could look like in the 21st century.